Response

This Amendment, Response and Request For Reconsideration is filed as the required submission for the accompanying Request for Continued Examination filed pursuant to 37 C.F.R. § 1.114. The Amendment, Response and Request For Reconsideration is responsive to the Final Office Action mailed May 15, 2009. Pursuant to 37 C.F.R. § 1.114(d), Applicants respectfully request that the Examiner withdraw the finality of that Office Action and enter and consider this Amendment, Response and Request For Reconsideration.

In the Final Office Action mailed May 15, 2009, claims 201-203, 205-209, 211, 213, 214, 220, 221, 224-228, and 230-233 were pending. Claims 203, 205, 208, 209, 211, and 214 were withdrawn from further consideration. Claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-233 were rejected under 35 U.S.C. § 112, first paragraph, and claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-233 were rejected under 35 U.S.C. § 103(a).

In the instant Amendment and Response, claims 202, 203, 205-209, 211, 214, 227, 228, and 230-233 have been cancelled, and claims 201, 213, 220, 224-226 have been amended. New claims 237 and 238 have been added. Following entry of the instant Amendment, claims 201, 213, 220, 221, 224-226, 237, and 238 are pending and presented for examination.

Claim 201 has been amended to incorporate the limitations of dependent claims 202 and 203. In addition, claim 201 has been amended for clarity. Claims 213, 220, and 224 have been amended in order to change the recited dependency in view of the amendment to claim 201 and the cancellation of claim 202. Claim 225 has been amended to correct a minor issue with antecedent basis. Support for new claims 237 and 238 is found, *inter alia*, in claim 205 of the application as filed.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

In view of these amendments, and further in view of arguments presented below, the Applicants respectfully request reconsideration and earnestly seek allowance.

The 35 U.S.C. § 112, First Paragraph Rejection

The Examiner has rejected claims 201, 202, 206, 207, 213, 220, 221, 224-228 and 230-233 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Specifically, the Examiner stated at page 5 of the Final Office Action:

> Therefore, support is not evident for a siRNA wherein the first and second nucleotides of the sense strand are 2'-O-alkyl and the rest of the nucleotides are 2'-OH, without the same schematic being present in the antisense strand.

Without acquiescing in this rejection, and solely in the interests of advancing compact prosecution, claim 201 (the sole independent claim remaining the instant application) has been amended to recite that the antisense strand also has a 2'-O-alkyl modification of the nucleotide closest to the 5' end and a 2'-O-alkyl modification of the nucleotide next closest to the 5' end, wherein all the remaining nucleotides in the antisense strand have a 2'OH. As the Examiner has recognized, such a pattern of modifications does find support in the specification as filed. Withdrawal of the rejection is respectfully requested.

The 35 U.S.C. § 103(a) Rejection

The Examiner has rejected claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-233 under 35 U.S.C. § 103(a) as being obvious over Giese et al (US 2004/0180351) in view of Elbashir et al (EMBO Journal, 2001, Vol. 20, No. 23, p. 6877-6888) and Vargeese et al. (US 2004/0110296). For the reasons presented below, the Applicants respectfully submit that the rejection does not properly establish a *prima facie* case of obviousness with respect to the pending claims.

With respect to Giese, the Examiner states at pages 13-14 of the Final Office Action:

> Therefore, Giese teaches to inactivate the sense strand via modifying the terminal 5' nucleotide; teaches that the antisense strand requires a 5' phosphate for function; teaches incorporation of combinations of the instant chemical modifications. Although Giese does not teach to specifically modify the first two nucleotides to inactivate the sense strand, it is certainly within the realm of routine

> optimization to extend the modification via one nucleotide, especially given that Giese teaches throughout the document that modifications are preferably incorporated in blocks one or more nucleotides. One would have been motivated to inactivate the sense strand via incorporating a block of modifications at the 5' end of the sense strand in view of Giese et al. Given that the resultant sense strand would be inactive, one would have been motivated to modify the rest of the sense strand with 2'-deoxy modifications given that Elbashir et al. teaches that 2'-deoxy modifications reduce the cost of RNA synthesis.

The Applicants respectfully disagree that one skilled in the art would arrive at the claimed siRNA molecules by routine optimization of the siRNA molecules taught in Giese and Elbashir. The claimed siRNA molecules have specific modifications of specific nucleotide positions that significantly reduce "off-target" effects in comparison to other siRNAs. More particularly, by virtue of the position and identity of the modifications recited in the instant claims, the off-target activity of both the sense and the antisense strand are greatly reduced, as stated at [0500] of US 2007/0167384, which is the published version of the instant application (emphasis added):

> When the antisense strand contains a phosphate group on the 5' end and is modified with 2'-O-methyl groups at positions 1 and 2, off-targets due to the antisense strand are lost, but sense strand off-targets are once again observed. Finally, when both the sense strand and the antisense strand are modified with 2'-O-methyl groups (on positions 1 and 2 of each strand) and a phosphate group is attached to the 5' end of the antisense strand, a drastic reduction in the level of off-targeting by both strands is observed.

Similarly, the instant specification states at [0501]:

> Thus, the combination of three separate modifications (5' phosphorylation of the antisense strand, 2'-O-methylation of positions 1 and 2 of the sense strand, and 2'-O-methylation of positions 1 and 2 of the antisense strand) leads to drastic reduction in off-target effects that are generated by both strands. In addition, in the three cases where specific silencing activity was tested (MAPK14, PTEN, and MPHOSPH1), the fully modified molecule (e.g., those that contain 5' phosphate on the antisense strand, 2'-O-methylation of positions 1 and 2 of the sense strand, and 2'-O-methylation of positions 1 and 2 of the antisense strand) that has minimal off-target effects, silenced the intended target as well or better than siRNA that contain only a 5'-phosphate group on the 5' end of the antisense strand.

Contrary to the position taken in the Office Action, the Applicants assert that the doctrine of routine experimentation and optimization are not applicable in the present case. MPEP 2144.05(II)(B), in its title, cautions: "Only Result-Effective Variables Can be Optimized." In the first sentence of that section the MPEP requires that "A particular parameter must first be recognized as a result-effective variable, *i.e.,* a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." Thus, in order for the doctrine to be applicable, there must have at the time been a known relationship such that the change in a variable led to a predictable result. However, the Office Action has not shown any teaching in the cited references that correlates the reduction of off-target activity of both the sense and antisense strands with specific modifications on specific nucleotides.

Furthermore, the Office Action has failed to establish a *prima facie* case of obviousness under *Eisai Co. v. Dr. Reddy's Lab,* 533 F.3d 1353, 1359 (Fed. Cir. 2008) (emphasis added), which explains that a finding of obviousness is appropriate only if: "(1) there is a starting reference point in the prior art from which a skilled artisan might identify a problem and pursue a potential solution; (2) there is some reason in the prior art to make particular modifications to achieve the claimed compounds; and (3) there was some reason for narrowing the prior art universe to "a finite number of identified, predictable solutions." The CAFC emphasized: "To the extent an art is unpredictable as the chemical arts often are, *KSR's* focus on these 'identified, predictable solutions' may present a difficult hurdle [when trying to establish a case of obviousness] because potential solutions are less likely to be genuinely predictable." *Id.*

The Office Action has not identified a lead compound in either Giese, Elbashir, or Vargeese, and has not identified reasons to make specific modifications to any compound and has not shown any degree of predictability in reducing off-target effects of both the sense and antisense strand during the relevant time period. Indeed, the cited references are completely silent with regard to the desire to reduce off-target activity of the antisense strand. As the Examiner recognizes, the modifications taught by Giese are intended to inactivate the sense strand, thereby reducing the potential for off-target effects caused by the sense strand. For example, at paragraph [0167], Giese states:

> Based on this observation the present invention reduces this off-target problem of siRNA by two approaches. First by reducing the molecule

> length of the siRNA molecules to the minimal requirements (18-19 nt) and thereby reducing the chance of homology to off-targets. Second, by inactivation of the sense strand to prevent a unwanted RNA silencing caused by accidental complementarity of the sense strand to a unrelated target RNA (see also Example 6).

Thus, because none of the cited references even recognize the problem of antisense strand off-target effects, one skilled in the art would not arrive at the claimed siRNA molecules through routine experimentation.

There are additional deficiencies in the teachings of Giese that are not remedied by either Elbashir or Vargeese. The Examiner states at page 9 of the Final Office Action (emphasis added):

> Giese teaches incorporation of various 2'-position modifications including amino, fluoro, methoxy, alkoxy, and alkyl (see paragraph [0024]). Giese teaches siRNA molecules wherein each strand comprises a plurality of groups of modified nucleotides having a modification at the 2'-position whereby each group of modified nucleotides is flanked on one or both sides by a flanking group of nucleotides, wherein the flanking group is either unmodified or is modified with a different modification than the modified group (see paragraph [0025]).

As the Examiner has recognized, Giese provides siRNA molecules in which either or both strands have a plurality of groups of 2' modified nucleotides arranged in the following fashion: each "group of 2' modified nucleotides" is flanked on one or both sides by a "flanking group of nucleotides." Each nucleotide in the "flanking group of nucleotides" is either unmodified or has a 2' modification different from that possessed by the nucleotides in the "group of 2' modified nucleotides." See [0025]. Each group of nucleotides comprises as few as one nucleotide. See [0030].

Because Giese requires that there be a plurality of "groups of 2' modified nucleotides" flanked on one or both sides by a "flanking group of nucleotides" each strand disclosed by Giese has at least two regions of modified nucleotides. See [0016]. For example, Giese discloses the pattern "MOMOMOMOM etc where M is a 2'-O-methyl nucleotide and O is a non-modified nucleotide." See [0124]. In this example, each M is a "group of 2' modified nucleotides" and each O is a "flanking group of nucleotides."

The siRNAs recited in the instant claims, by contrast, do not comprise a plurality of "groups of 2' modified nucleotides" flanked on one or both sides by a "flanking group of nucleotides." By contrast, the instant claims recite that only the first and second nucleotides on the sense and antisense strands are 2'-O-alkyl modified and that the remaining nucleotides are unmodified at the 2' position, i.e., the remaining nucleotides are 2'OH. Using Giese's nomenclature, the sense and antisense strands of the claimed siRNA have the following modifications: MMOOOOOOOO etc. In other words, there is only a single group of modified nucleotides on each strand of the siRNA recited in the claims. The Examiner has not provided any reason why one skilled in the art would ignore Giese's requirement for a plurality of groups of modified nucleotides such that only a single group of modified nucleotides is present on each of the sense strand and antisense strand, nor has the Examiner provided a reason for positioning those modified nucleotides at the specific locations recited in the instant claims. Furthermore, neither Vargeese nor Elbashir provide a reason to make such modifications to the molecules of Giese.

The Applicants reiterate that Giese actually teaches away from the siRNAs recited in the instant claims. At paragraph [0123], Giese states "In a preferred embodiment the second (penultimate) nucleotide at the terminus of the strand and stretch, respectively, is an unmodified nucleotide or the beginning of group of unmodified nucleotides." Giese goes on to disclose that when the penultimate 5' nucleotide on the antisense strand is 2'-O-Me modified, the resulting siRNA is non-functional. See Example 11, Figures 16A-16C and [0193]-[0194]. Similarly, at paragraph [0173] Giese states "[t]his leads to the conclusion that any end of the antisense strand and more particularly the 5' end of the antisense should be kept without modifications." Contrary to the Examiner's assertion, these statements from Giese cannot be interpreted as merely expressing a preference for a lack of modification at the 5' end of the antisense strand. Rather, these statements are a clear warning that a non-functional antisense strand will be obtained if the 5' end of the antisense strand is modified. The siRNA molecules of the claims include a 2'-O-alkyl modification at the two 5' terminal nucleotides of the antisense strand, and thus include modifications at the very position that Giese warns against modifying. Hence, Applicants respectfully submit that Giese does indeed teach away from the claimed siRNA molecules.

The Applicants respectfully point out that the Examiner appears to have misinterpreted the claim term "2'-OH" as referred to a "2-deoxy modification." For example, the Examiner states at pages 13-14 of the Final Office Action:

> One would have been motivated to inactivate the sense strand via incorporating a block of modifications at the 5' end of the sense strand in view of Giese et al. Given that the resultant sense strand would be inactive, one would have been motivated to modify the rest of the sense strand with 2'-deoxy modifications given that Elbashir et al. teaches that 2'-deoxy modifications reduce the cost of RNA synthesis.

Furthermore, the Examiner also states at page 16 of the Final Office Action:

> Modifying the remainder of the strand with 2'-deoxy modifications is a newly added limitation which necessitated this new rejection and is addressed by Elbashir et al, wherein Elbashir et al teaches that 2-deoxy modifications reduce the cost of RNA synthesis. Given that Giese et al sets forth the motivation to inactivate the sense strand via terminal modification, one of skill would have certainly been motivated to incorporate 2'-deoxy modifications in the rest of the strand to reduce RNA synthesis costs.

One skilled in the art would understand that a 2'-deoxy modification refers to a nucleotide having a 2'-H (as in DNA). The claimed siRNA molecules possess 2'-OH (as in unmodified RNA) at all nucleotide positions other than the two terminal nucleotides at the 5' end of the sense and antisense strands. Hence, the teachings of Elbashir with regard to 2-deoxy modifications are not relevant to the siRNA molecules of the claims.

In summary, for the reasons provided above the combination of Giese, Elbashir, and Vargeese does not teach or suggest the claimed siRNA molecules. Withdrawal of the 35 U.S.C. § 103(a) rejection is respectfully requested.

Conclusion

This Amendment fully responds to the Final Office Action mailed on May 15, 2009. Still, the Office Action may contain arguments and rejections that are not directly addressed by this Amendment because they are rendered moot in light of the preceding amendments or the preceding arguments in favor of patentability. Hence, failure of this Amendment to directly

address an argument raised in the Office Action should not be taken as an indication or admission that the Applicant believes the argument has merit. Furthermore, the claims of the present application may include other elements, not discussed in this Amendment, which are not shown, taught, or otherwise suggested by the art of record. Accordingly, the preceding arguments in favor of patentability are advanced without prejudice to other bases of patentability.

Applicants respectfully submit that the present application is in condition for allowance and solicit a notice to the effect. If the Examiner believes that allowance can be advanced with a telephone conference, the Examiner is invited to telephone the undersigned at the number provided below.

This constitutes a petition for an extension of time if one is not specifically requested. Payment of appropriate fees by credit card accompanies this filing; however, if any additional fees are due, the Director is authorized to deduct said fees from Deposit Account # 13-2725.

Respectfully submitted,

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